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T H E S I S

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" H Y P N O T I C S "

WITH SPECIAL REFERENCE TO THOSE OF
MODERN INTRODUCTION.

for the Degree of M. D.

B Y

W I L L I A M C H E Y N E W I L S O N

M.B.,C.M., 1885.



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1.

"HYPNOTICS"

WITH SPECIAL REFERENCE TO THOSE OF
MODERN INTRODUCTION.

In endeavouring to select a subject worthy of the traditions of my Alma Mater I was struck by the great advances made in modern Pharmacology and Therapeutics, and especially in the matter of the introduction of new remedies, amongst which are to be found so many which owe their prominence to the fact that they are more or less hypnotic in their action and so I thought that by reviewing the hypnotics generally and by analysing the effects of some especially I might thereby add something to our stock of medical knowledge however small that addition might be.

That sleep, "tired Nature's sweet restorer" has been regulated and induced for many ages is evident on reference to the writings of those philosophers

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and physicians who have handed down to us records of their times. For example, if we peruse the only great work which survives, the great Latin writer and physician, A. Cornelius Celsus, we find in his *De Medicina*, reference concerning those things which are fitted for sleep.

(1). "Somno vero aptum est papaver, lactuca, maximeque, aestiva, cujus cauliculus jam lacte repletus est, morum, porrum. Sensus excitant, nepeta, thymum, satureia, hyssopum, praecipueque pulegium, ruta et cepa. " to whom next to Galen and Hippocrates we owe our knowledge of the medicine of antiquity.

To come to much later times we find, for example, in Gregory's *Conspectus Theoreticae Medicinae* that physicians often try to regulate sleep.

(2). "et ope quarum medici saepe conantur neque frustra, temperare somnum prout res postulaverint." and still further, that there are things, which applied to the body or received into it bring on deep sleep, and of this sort are what are called narcotic remedies. (3). "Denique sunt res quae admotae corpori

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aut receptae in id ipsum non modo, non excitant nervosum genus, sed plane sopiunt, reddunt minus aptum ad sensum que motum, et sic inducunt altum somnum.

Hujusmodi sunt quae vocantur narcotica remedia, opium et similia; quibus oportet annumerare vinum ipsum sumptum nimia copia et quosdam lethiferos vapores, veluti ardentis carbonis."

Between these two epochs, A.D. 50 & A.D. 1792, we may trace many instances where medicines have been used to produce narcosis and in not a few - where the names of the drugs are given - we find that Opium is the most prominent of those which are still used in the present day, the greater number of the remainder having fallen out of use either from their having a very feeble action or not possessing any hypnotic effect at all.

In selecting the various drugs which either have or are being used as hypnotics it is not my intention to dwell at any length on those which have been before the profession for a long period and whose physiological actions are very well known,

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except to point out any advantages or disadvantages which they severally possess.

One naturally in the first instance selects Opium, the most highly prized of the various members of the narcotic group and up to the introduction of those substances which may be called "pure hypnotics" and to which I shall draw special attention later - as it is to these that I more especially wish to dilate upon - with very few exceptions, this was the drug resorted to in order to produce sleep.

The narcotics, as a group, are bound always to occupy a very prominent position as remedies for insomnia, because there are many forms in which pure hypnotics are useless and as Opium stands foremost in this group, one feels justified in prophesying that in sleeplessness caused or accompanied with pain it will ever occupy a premier position, for with the forward march in modern therapeutic remedies not one of the pure hypnotics seems to have any effect in the relief of pain and unless the ever widening "Newer Pharmacopoeia" introduces us to some such drug the

position of opium is assured.

As pain is so often a cause of sleeplessness there is no better weapon in our armoury than Opium to meet this condition and in this state and possibly also in the insomnia of delirium tremens, its action seems to be most indicated and as it is not my intention to discuss the narcotics at any length, I would do no more than point out the advantages of this drug in this perfunctory manner. Although we may claim these undoubted advantages for it what we can say on the other side of the balance? When a physician has recourse to any drug for the relief of insomnia he must always have the fear constantly pictured before his mental gaze that the drug he may use may be one that may create a habit in the patient and thus enslave him for life, perhaps, to its action, and the most casual observer cannot shut his eyes to the fact that of all the medicaments for which a habit may be created, Opium & Morphia occupy a very prominent position, and as the danger is so great one may readily formulate a rule that in simple

chronic insomnia, not accompanied with pain, Opium and its alkaloids should never be given. I have been so impressed during the ten years I have been in practice not only of the possibility but also with the actual fact of its occurrence - for I have met with a number of cases so induced, one of which ended fatally, that I never by any chance would be induced to prescribe them in such a condition - but on the other hand, should the insomnia be of very short duration and of a fleeting character as it were, by which I mean that it was not likely to be repeated, Opium might be used as advocated by Whitla (4) in his Dictionary of Treatment, although I should much prefer one of our modern hypnotics.

Then of the other disadvantages - it is hardly necessary to point out how badly it is borne by children, how it produces constipation, and how it is contra-indicated in congested states of the brain, bronchitis with profuse expectoration, and the late stages of Phthisis. As regards its use in uraemic conditions, opinions differ greatly; for although it

used to be generally acknowledged that it was never to be employed in such cases, some authorities now assert that it is safe; Indeed Osler goes so far as to say that it is indispensable in the restless and delirium and such men as Mackenzie uphold its use. Whitla (5) also states that recent experience shows that the hypodermic injection of morphine may be beneficial in uraemic convulsions, and again according to Ringer (5a) Scanzoui "finds it very useful in uraemic convulsions." On the other hand, Fagge (6) and Burney Yeo (7) state that a rapidly fatal result has followed the use of a small dose of opium in chronic Bright's Disease. On the face of such conflicting opinions I think we may dismiss the subject with the remark, that it should only be given by those who have had great experience in this troublesome disease and who have great confidence in its usefulness and even then I fear lest the quiet induced by it may be that sleep out of which there is only one awaking.

Of the Alkaloids of Opium I need only refer to Morphine, Narceine, and Papaverine, as the remainder are either only very feebly hypnotic or possess

no hypnotic action at all.

As the actions of Morphine are almost identical with those of Opium and as it is open to precisely the same objections it can be passed over after emphasising the differences. In the first place of course it is more agreeable to the palate, again it seldom produces headache, excitement, nausea, or constipation, it is also less stimulant in its effect and therefore is a purer hypnotic and of course is much more suitable for hypodermic injection. The bimeconate produces very little after ill-effects and is therefore its preferable salt. Again, morphine in common with other of the Opium Alkaloids has both a convulsant as well as a hypnotic action, hence a combination of Methyl and Morphine has been produced in order that the former action may be minimised, for a number of Methyl compounds have well known hypnotic and analgesic actions. Salts of the resulting Methyl-Morphine (8) lose all trace of convulsive action but retain the hypnotic power of Morphine. Papaverine according to Leidesdorf is soporific and

narcotic and Whitla (9) states it to be highly hypnotic. Ringer (9a) says "It is said to possess strong narcotic properties without producing the previous stage of excitement and is not followed by headache and giddiness." But it also reduces the pulse and as it has been so little used it is difficult to pass an opinion on its merits, for I have never used it myself and can find little recorded concerning it; but in face of its depressing action on the circulation I think we may fairly discard it in favour of the more modern hypnotics whose actions are fairly well understood and which have stood the test of a larger and more extensive trial.

Narceine. The properties of this alkaloid seem not to be well understood. By some it is reckoned as a hypnotic of undoubted value whilst others consider it to be almost inert. It is difficult to reconcile such contradictory opinions but they are probably the result of the fact that it is a substance that has been so seldom used that it has not always been produced perfectly pure which may account for its giving

actions totally different in the hands of different observers, but I cannot help thinking that the weight of opinion is decidedly in favour of its being a hypnotic of great value, although in some cases - as with opium - it does not affect to the same degree. Its advantages seem to be that it does not cause those after effects, such as headache, etc.; but on the other hand it is so very insoluble that it is of no use for hypodermic medication. In support of its action we have such authorities as Harley, for Garrod (10) states that "Harley finds it a pure hypnotic, much feebler than morphine" and Ringer (11) also voices the opinion of Harley in these words "Dr J. Harley considers narceine a pure hypnotic." Then again Claude Bernard concludes its narcotic action is superior to morphine, in dogs at least. Whitla (12) also states that it is "highly hypnotic" and Phillips (13) again says that "The substantial agreement of all the best French Authorities, (Claude Bernard, Belvier, Delpech, Bouchardat. fils) with two of the best German experimenters, Erlenmeyer & Eulenberg, com-

pletely disposes of the idea that Narcein is an inert, or nearly inert, substance; on the contrary, it is plainly a hypnotic of considerable power, though it fails to affect some individuals, and is comparatively free from the tendency of opiates to produce after headache."

On the other hand Bentley(14) says "It is feebly hypnotic" and Dr Frommüller, having tested it by mouth and hypodermically asserts that it possesses no narcotic properties and that a dose of 20 grains by the stomach produced no sleepiness or effect on other organs. Garród(15) also states that "it is useless as a medicine."

The lactate is very soluble and Husemann suggests that this salt should be used as its high insolubility may have something to do with its having little or no effect.

Meco-Narceine - which I believe is a combination of Meconic Acid and Narceine is the name of a new hypnotic alkaloid of opium which Laborde said produces no headache or gastric disturbance.

Perhaps before leaving the alkaloids of Opium I should state that Meconine or Opianyl (the other neutral body in opium besides Narceine) is said to act on man as a mild hypnotic and all authorities seem to be agreed on this point, for Garrod and Bentley both claim for it this action - the former stating that it is superior to Narceine.

The remaining alkaloids are either inert, or have a strychnia like action and so I need not refer to them.

I think that on taking a survey of opium and its alkaloids we may safely say that neglecting those cases of insomnia which are caused by painful disease they are not to be desired as their disadvantages greatly overbalance their advantages in habitual cases of sleeplessness, provided that further investigation of some of its alkaloids - a thing much to be desired - does not prove that one or more of these alkaloids, when produced chemically pure, have all the advantages of the parent drug but with none of its disabilities.

Burney Yeo (16) I think very fitly sums up the case when he says that "we need not refer to the value of opium for the relief of insomnia due to painful disease, We have already repeatedly dwelt on that subject and we have only to say here that it is, of all the means at our disposal, the least desirable for the relief of the habitual cases we are now considering."

In the next instance I would wish to draw attention to Alcohol. Speaking broadly we may say that of all the drugs which are used as hypnotics there is probably not one so valuable as this to produce sleep. As is well known it has well marked narcotic properties and were there no danger of producing the alcoholic habit, I think we would find it one of the best hypnotics at our command. Of the various beverages containing Ethylic Alcohol we find that many have actions which vary greatly and which cannot be explained by the percentage of this drug which is contained in them which is probably due

to the various Ethers which are developed by maturation of the liquid and possibly by many impurities which may be present. Whiskey is undoubtedly much superior to either Rum or Brandy - and as far as that goes than any of the Wines, to produce sleep - and strong Ale and Stout are highly hypnotic in great measure due to the hops they contain. In cases where the patient refrains from taking alcohol except when ordered by the physician, the hypnotic effects are more marked and also the same dose seems to produce the same degree of effect for considerable time without any augmentation being required - a fact that must have forced itself under our notice on many occasions. In order that the best hypnotic effect of alcohol may be produced it is always advisable to give one dose - about two and a half ounces of good whiskey - with warm, not hot, water while the patient is undressing, so that the preliminary stage of excitement shall have passed off by the time the patient retires to rest and moreover the whole quantity should be swallowed at one draught or nearly so, and not in small sips as is so

often done, in order that the full effect of the drug may speedily assert itself; but should the physician have reason to suspect that the habit would be induced he might add to it some strong bitter or perhaps better withhold it altogether.

I might state that Hop also has hypnotic power and that we can combine the two in the form of strong ale or stout or by adding some of the Tinctura Lupuli to the Whiskey, or else give 1 to 4 fluid drams with an aromatic water as suggested by Burney Yeo (17) or with pure Alcohol itself. Beyond this slight reference to Hop I shall have nothing further to say.

To sum up, Alcohol seems to be a hypnotic of some power and to be indicated in such cases as a transient insomnia - such as that produced by Neuralgia, or overwork - but most certainly not to be employed in obstinate cases, provided there be no dread of inducing chronic alcoholism, a state which seems not likely to be induced provided the physician's directions are strictly followed, and I feel perfectly certain of the fact - from my own experience - that

the danger of intemperance is much greater when alcohol is given in smaller quantities and oftener.

Whitla (18) gives the same as his opinion for he says "the writer has not met with an instance when the patient has suffered when the drug has been given with the above named restrictions. The danger of intemperance is much greater when the alcohol is ordered in small quantities to be taken with meals."

Cannabis Indica need not detain us long for as far as present experience goes it seems to have all the disadvantages of Opium whilst it does not possess all its advantages therefore does not seem suitable in simple insomnia. When first introduced this drug seemed to afford those who first used it grounds for belief that it was a substance of great merit but fuller acquaintance with it has not supported the expectations then formed, and as regards the actions to which I am recording an opinion it certainly is disappointing. It seems to be superior to Opium in respect to its effects on digestion, as it does not

cause loss of appetite nor constipation, and headache also is rare after its use. There are some who are strong advocates for its use in simple insomnia and Phillips (19) states that Dr Glendenning who has employed it extensively says "conciliatory tranquil repose without causing nausea, constipation, or other signs or effects of indigestion, without headache or stupor," follows its use. I have only used the drug occasionally myself and I do not feel the same confidence in it as appears in this quotation, and although it has received such unqualified praise by Dr Glendenning and others I feel that until we know more about its action and that of its alkaloids, we should at least give preference to these drugs of which we know considerably more. The great objections to its use are, its uncertainty and irregularity of action, and also that it requires a large dose to obtain its full hypnotic effect. In respect to the first point I would draw attention to the fact that out of 1000 cases treated by Frommuller (20) it succeeded only in 530 cases, partly succeeded in 215 and produced little

or no effect in 255 instances, which one can hardly regard as satisfactory; and in the second place he stated that he found a large dose always necessary to produce its hypnotic effect, in fact in his cases, he says, he used as much as 8 grains of the spirituous extract, although of course the extract he used must have been much weaker than ours for we often get unpleasant effects with even less than $\frac{1}{2}$ grain. I think that the unreliability of its action must to a great extent depend upon the fact that often a very inferior hemp is imported and used. Should insomnia depend on Chorea, Delirium tremens, or Neuralgia, Cannabis Indica may be advantageously tried, for most authorities agree that it has given gratifying results in these cases. Some also claim its use in the insomnia of mania but I think we have a much more efficacious drug in Hyoscine.

Of the alkaloids of Cannabis Indica I can only find records of two being used, viz, Cannabin, and Cannabinon.

Cannabin Tannate is the salt usually employed and according to Prof. Leech (21) it is the best preparation of Cannabis Indica. Frommuller recommends it in five to ten grain doses as hypnotic. It does not seem to produce any unpleasant toxic effects and it is said not to cause any intoxication." It causes calm and natural sleep"(22). If all these statements are confirmed by subsequent investigations I think we may extend to it a far larger patronage than it at present receives, as it seems only to have been used by a few.

Cannabinon. only deserves a passing notice, It has, I believe, been tried by Richter and others and is stated to be more certain and powerful than the previous alkaloid, but beyond this I know nothing about it.

The Bromides. All have almost similar hypnotic effects and those of Potassium and Sodium seem to be the best. Some authorities recommend one salt and others another; some also have a preference for Hydrobromic Acid and the least that can be said about it is that there it is the least objectionable in order to get

the effects of the Bromides - for it very seldom causes any gastric trouble and it certainly has none of those depressing effects which are associated with the potash salt and which are caused by the base in the salt. Of the salts that are used, that of Sodium is the best for it has much less influence on the heart, and it is not so irritating to the stomach as the other bromides. The precise form of insomnia in which the bromides are specially indicated seems, at present at least, a matter of speculation, for from all the literary matter on the subject that I am acquainted with, authorities are anything but agreed, some strongly advocating it in one special variety whilst others recommend it in another and I am entirely at one with Garrod when he says (referring in his case to the potash salt) (23) "It is still a desideratum to discover the exact form of sleeplessness which is relieved by this remedy." but although there is some divergence of opinion in regard to the salts and the forms in which they are most suitable, I think I ought to point out the several forms, where my experience con-

firms those of other observers. In the first place where want of sleep arises from prolonged mental exercise or from worry, anxiety or grief, the bromides I believe to be invaluable. Here we are dealing with cases of over mental activity and not mere simple wakefulness, where the cyclitic functions of the brain are going on rapidly, where we have a rapid succession of ideas which are often very brilliant in their conception, and which are accompanied with hyperaemia of the brain, in all probability, where other signs of congestion are often present such as throbbing in the head, flushed face, etc., Here a fair dose, such as 30 grains of the Potash salt, often acts like a charm. Then there is a second class of cases, quite different from the above, which one might term "nervous insomnia", and which have been aptly called by Dr Clarke "a sort of hyperaesthesia or nervous irritability" when the person - who is generally of a highly nervous disposition - soon after getting in bed is constantly on the move making ineffectual efforts to be comfortable, where the slightest

stimuli seem to cause marked effect, the least light or an accidental noise of a slight nature, prevents him becoming quiescent, in fact where the whole nervous system seems, if I may use the phrase, to be on the alert, and responds to the smallest of external stimuli. In this class of patients there is no remedy that I know of that is equivalent to the bromides, whose effects probably depend on their action in influencing reflex excitability. Lastly I believe bromides in large doses are of great service in the insomnia of delirium tremens, either given alone or in conjunction with some other drug.

Where the bromides are used it often happens that they completely fail in very severe cases and this has been attributed by Dr Clarke to their action of producing anaemia of the brain. He says that sleep is caused by a moderate amount of anaemia but wakefulness on the other hand is the outcome of either excessive anaemia or of hyperaemia of the organ and on this theory he based the effects of the bromides on himself and thus after great mental fatigue, which he says

causes anaemia of the brain, forty or even fifty grains of bromide caused insomnia, although it soothed and quieted him; but when on the other hand he was wakeful as the result of an ordinary amount of brain fatigue it always produced profound and refreshing sleep. Whether such a theory holds good I cannot say, but it at least explains, should it be correct, those cases which one now and then meets of its failure in very severe cases. The great advantages of the bromides are that we seldom get ill effects following their action and I heard it stated not long ago by a eminent physician that, although he had used the drug very largely, and often in very large doses, he never had a case where symptoms of poisoning had manifested themselves and as far as I have been able to trace the number of deaths from the bromides are extremely few indeed, in fact it seems to be a "rara avis", and thus one almost begins to look upon it as non-poisonous. Then again they can be taken for very long periods without hurt and in most cases without any augmentation of the dose.

Whitla (24) records a case of a patient, with a bad family history of insanity, who suffered from sleeplessness, where Bromide of Potassium was administered along with a small dose of Tincture of Hyoscyamus every night for a period of 25 years without producing any ill effects.

Hyoscyamus. Although a drug which has for a long time been used as a hypnotic is seldom now employed for this action alone. It is sometimes found useful to combine it in small quantities with the bromides. Its chief application now seems to be its substitution for opium, where this latter drug either disagrees with the stomach or is contra-indicated. Firstly, it has little or no constipating action, even in large doses and so is preferable to opium where constipation is a troublesome accompaniment; but at the same time it seems to increase the narcotic action of opium when combined with it and so it is found useful sometimes to order both together.

Again, children bear enormous doses of it

and it is therefore decidedly preferable in diseases of children as a hypnotic. It is also very useful in cases of delirium where there is great excitability of the nervous system but where it is accompanied by little or no cerebral congestion and lastly it can be given in irritable conditions of the kidneys as it is a mild diuretic. So we might broadly state that it is the drug which will replace opium in these conditions in which the latter drug would be given were it not for certain contra-indications. Although Hyoscyamus is not now often prescribed as a hypnotic, its active principles are very often used. Unfortunately the nomenclature, actions, etc., of the alkaloids is very confusing, probably due to the fact that they have not been very deeply investigated and that when they were first introduced those who worked with them did not use pure alkaloids.

As far as I am able to discover there are two distinct alkaloids, the one Hyoscyamia occurring in an amorphous form when not pure, as often seen in such condition commercially, but occurring in crystals

when perfectly pure; and the other Hyoscina which always occurs amorphous. Both these alkaloids form salts, of these, the Sulphate of the first, and the Hydrobromate and Hydrochlorate of the second are generally used as they are found to give the best results. They are almost always given hypodermically.

Hyoscyamia is isomeric with atropine and identical with duboisine and daturine and the crystallised Hyoscyamia resembles atropine closely in its action, but it is also hypnotic. Wills has obtained this alkaloid from Belladonna, and according to him (25) it can be changed into atropine by keeping it heated to the temperature of its melting point or by treating it with a trace of alkali. It is necessary to emphasize the distinction between the crude commercial article and the pure crystalline body, for the dose of the former is given by Dr Lauder Brunton as $1/60$ to 1 gr. now such a dose of the crystallised product would most certainly cause death and on no account should the maximum dose of $1/20$ grain of pure sulphate of Hyoscyamia be exceeded hypodermically. Hyoscyamia is

not so often used now as the other alkaloid as a hypnotic, nor in fact for any of its other actions for it seems to be generally feebler, especially is the this case as regards producing sleep. Whitla (26) states that it is occasionally used but as a hypnotic it is inferior to Hyoscine. Landenburg was the first to investigate the alkaloids of Hyoscyamus and they were further investigated by Prof. Wood. Dr Robert Lawson of the Third Middlesex Asylum, has found it of great service as a hypnotic in mania where aggressive excitement was the leading symptom and he says that it substitutes a mild for a more active delirium. He gave it in doses of one grain to one grain and a half (presumably of the crude alkaloid) and found it produced sleep in about fifteen minutes lasting from ten to twelve hours after which the patient awoke free from delusions. This dose seems to have caused some alarm to the patients' friends and to Dr. Lawson and I believe he recommends a smaller dose now. In the insomnia of mania it is undoubtedly with the exception of Hyoscine the best drug we possess and it is much

superior to either Morphia, Atropine, Ethyl-Atropine, or Daturine in these cases.

A very fine comparison of the efficacy of these drugs is reported by Ringer (27) of a case which occurred at University College Hospital of a nurse who was seized with mania accompanied with insomnia, which was so pronounced that it threatened her life. Morphia was tried unsuccessfully, although it was given at last in such large quantity as $\text{Ms. } 100$ divided into three doses, but the first dose of Hyoscyamia gave relief by producing $15\frac{1}{2}$ hours sleep and ultimately the case recovered.

Hyoscina was the name given to the second alkaloid of Hyoscyamus by Ladenburg. It was first named Sikemaine. It has also been called Amorphous Hyoscyamine. Whether it is identical with the amorphous crude form of Hyoscyamine or not I cannot say but I think not, as by some it is stated to be an amorphous powder whilst others state that it is of a syrupy consistence. Its salts can now be obtained very pure and a dose of $\frac{1}{100}$ grain of pure Hyoscine is generally

strong enough hypodermically for the most stubborn cases. The Hydrochlorate is generally given in doses of $\frac{1}{120}$ gr. and the hydrobromate of $\frac{1}{200}$ gr., in both cases hypodermically. There is another salt, viz., the hydriodate but it is seldom or ever employed. This alkaloid has been thoroughly tested and seems to have come out of the ordeal very well. It seems to be specially indicated in the insomnia of mania, delirium tremens, and all cases of sleeplessness accompanied with mental excitement. Prof. H. C. Wood, of Philadelphia, was I believe the first to experiment with it. He found in insomnia, the result of too great cerebral activity and in intense fever accompanied with delirium it was decidedly of great benefit. From that time onwards almost every pharmacologist has used the drug and all have little but praise to bestow upon it.

Mitchell Bruce (28) says that it is a powerful cerebral sedative which very rapidly and completely controls those conditions of cerebral activity known as delirium, mania, and insomnia with restlessness, proving useful in the delirium of pneumonia, cardiac

and renal disease, and that it is a remedy which can readily be administered and will act immediately and for several hours afford quiet and rest, not only to the patient but also to those around him. Nestor Tirard considers it can be given with perfect safety in kidney disease where morphia is inadmissible and that it gives rest when other sedatives fail and according to Whitla (29) Tirard injects 1 to 2 min. of a 5 per cent solution. Dr Henry Wetherill, Junr., of Pennsylvania Hospital for the Insane, says the hydrobromate proved highly satisfactory in cases of great motor activity in chronic insanity. He states (30) that "It is no exaggeration to say that the excited wards have entirely changed in character for the better since the introduction of Hyoscine and its beneficial results in acute cases have been very encouraging."

After making very extended trials in mania and insomnia Malfilatre & Lemaire (31) have proved it to be one of the most reliable hypnotics in these cases.

(32) Messrs Lefort & Magnan found that $\frac{1}{60}$ gr.

in five minutes caused the patients to lose morbid activity and to sleep for five or six hours without any inconvenience. It was also used very successfully in delirium tremens.

Sohrt (33) produced in more than one hundred cases of lunatics, in whom chloral hydrate, bromide of potassium, paraldehyde, hyoscyamia, were inert, by injecting $\frac{1}{120}$ gr. to $\frac{1}{60}$ gr., sound sleep after ten or twelve minutes, which lasted from five to eight hours without any ill effects, the only thing being that some patients complained of slight headache in the morning.

Lionel Weatherley (34) recommends it to be given by the mouth as he says that when it is given hypodermically it produces stupor sometimes and leaves the patient ~~sometimes~~ as bad as ever afterwards; but it is successful in delirium tremens. He thinks it is not a safe drug and looks upon its indiscriminate use as a powerful and sudden hypnotic an abuse, but he thinks it a valuable agent in experienced hands. He also thinks it useless in hysterical

cases with hallucinations.

(35) Barling employed it extensively in delirium tremens, acute mania, and the delirium of heart disease and no bad effects were observed. A remedy which has been extolled by so many observers is one that should find a place in our pharmacopeia, because it is doubtless a very powerful and certain calmative and hypnotic and which seems not to have a depressing action on the heart and is further of great service in that it can be used in renal disease. I have not had great experience with the drug but in the few cases I have used it I feel certain that it is a drug which deserves fuller recognition. One case especially forces itself upon my memory. I was called in consultation by a brother practitioner to see a case of insomnia where there was a latent strain of insanity and it was further complicated by the fact that puerperal eclampsia manifested itself. I suggested the use of Hyoscine hypodermically with a result which even exceeded my rather sanguine expectations. Although there is so much to be said in praise of the

drug we should remember that cases have been recorded of poisoning by it. Whitla (36) states that sharp depressant effects have followed $\frac{1}{60}$ grain and he further states that valvular disease is a contra-indication to its use; but as regards the latter I think it wise not to come to too hasty a conclusion for I am of opinion that some of these cases of alarming symptoms are due to the fact that Hyoscine is not always pure or else that Hyoscyamine is given instead through the confounding of the two alkaloids which, as I have already pointed out, was of common occurrence when they were first introduced. Then the question naturally arises "If we have such a powerful and reliable remedy as Hyoscine, why is it that it has not been more generally adopted in this country?" and I think this can be very satisfactorily answered, because it is so very often confounded with Hyoscyamine, a drug which has not presented such a harmless record and many having used the latter and having abandoned it on account of its sometimes dangerous effects have at the same time given up using the Hyoscyamus Alkaloids altogether - possibly under a

misapprehension of the fact that there are two distinct bodies in the plant.

Dr Drapes - the Resident Medical Superintendent of the District Asylum, Enniscorthy - in 1889 in a report (37) of his experience of two years with Hyoscine, besides supporting all that has been said previously in this essay, states that he believes many have abandoned the use of Hyoscine from the fact that it has constantly been confounded with Hyoscyamine which cannot be said to present an innocuous record and which on account of the dangerous symptoms which have been observed to result from its action has been discarded, and being under the erroneous impression that the two drugs were identical have refrained from the use of Hyoscine.

Although Hyoscine is usually given hypodermically some advocate its use by the mouth. Webber gives it in this manner in insomnia in doses of 20 mins. of a solution of the hydrobromate containing one grain in a mixture of Spt.Vini.Rect. 3iss and Aqua ad 3XX, or it might be given as Whitla suggests, in 3j doses each containing $\frac{1}{48}$ grain of

Hyoscine Hydrobromate (Merck) in water with a little Tincture of Orange.

Chloral Hydrate since its introduction by Oscar Liebrich has been very extensively used and before the introduction of the many newer remedies, it was probably more often used than any other drug except Opium.

Either in cases of simple insomnia or that accompanying delirium tremens it is doubtless one of the most certain soporifics we possess if pain be not present; but as an anodyne it stands far inferior to either Opium or Morphia. It does not act as Liebrich supposed by being decomposed in the blood by the alkali in this fluid into Chloroform, for the odour of Chloral or Chloroform does not appear in the breath even after large administrations and this theory moreover has been thoroughly confuted by the experiments of Hammersten, Amory, Lewison, and Rajowsky. Although so certain in its action it has two very great drawbacks to its use, and these are so great that it never will be used as a routine drug, and it is being used

less often every day and this fact has been very well exemplified in my own family. I remember very well, when I was apprenticed to my late uncle over fifteen years ago it was constantly being prescribed by him, so much so that I was of the opinion that it was almost as great a necessity as opium to a physician, but as time went on I found he used it less and less and my late father often used to mention how in his earlier days he was constantly using it but that as time rolled on he had not so much trust in it, so that during the last few years of his life (he died a little over twelve months ago) he hardly prescribed it at all; and during the ten years I have been in practice I have found that I have seldom or ever resorted to it and I know that my experience is that of those who can look back a few years. It acts rapidly but unfortunately it depresses the action of the heart by paralyzing the cardiac ganglia and it also causes the temperature to fall greatly, this latter action being sufficient, as demonstrated by Brunton by his experiments on dogs, to cause death. Then also the chloral habit is ~~also~~ very easily established, even more eas-

ily than that of Morphia or opium and with two such unfortunate qualifications as these I think we would be wise only to use it in exceptional instances. In the many cases of chronic sleeplessness I feel the temptation is often very great to use a drug which gives such uniform and certain effects; but we should remember that although patients may be able to take the drug with impunity and with seeming advantage for a long time yet there is always a possible remote chance that it may cause death when little expected, and especially is this the case when there has been an augmentation of a dose; although the previous dose had seemingly produced no ill effects.

There seems to be no certain data ~~which we give~~ which will guide us to say in what cases it will depress the heart, for it is unreliable in its effects on this organ, as our obituary notices often demonstrate to us and in the face of such facts I would never be tempted to use it except exceptionally and I feel certain that the days of Hydrate of Chloral are numbered most certainly as a general hypnotic.

If given it is best employed in conjunction with the Bromide of Potassium or Sodium as its action seems to be intensified by them and a much less dose is then required and the risk of ill effects greatly diminished. Some advocate its combination with Morphia and indeed I well remember that it was a routine practice of my late uncle many years ago, my late father at one time also gave this combination, but many authorities say that it is one of the most dangerous hypnotics possible and in the face of this one cannot recommend such combination unless these statements can be refuted and my experience bears out their testimony as I have a distinct recollection of more than one case of dangerous symptoms arising from this cause during my apprenticeship.

The only cases of insomnia which to my mind are suitable for the exhibition of Hydrate of Chloral are those of delirium tremens, where the Bromides have been tried and failed, when the combination of the two often produces refreshing slumber and in these cases it should only be given in the

early stage of the disease and where the heart shows no sign of degeneration or weakness. In the latter stages of this complaint it seems to be absolutely dangerous, as the heart is peculiarly susceptible to its action and Whitla (39) states that the use of chloral in this disease raises its mortality, and "he now only uses it with fear and trembling when every other means fail, which is very seldom."

This depressing action on the heart has been tried to be counteracted by uniting it with other remedies which form new compounds and we owe a number of our newer hypnotics to these combinations to which I shall refer later on.

I should in justice to Chloral quote the paper of Professor Bartholow of Cincinnati (40) on a combination of morphine, atropine, and chloral, but as this was written before the introduction of the newer remedies I think with even such a strong recommendation as was here given, we are justified in preferring some of these remedies to chloral even in a combination such as this. "In man the excitant

action of atropine hinders the occurrence of chloral narcosis, but rather deepens the sopor when it at last supervenes. The effects of atropine last much longer and are apparently in no way prevented by Chloral. Morphine deepens in every the effects of Chloral. Many of the unpleasant effects of Morphine are modified as regards the wakefulness caused by the latter, but are not modified as regards the subsequent nausea, vomiting, headache, vertigo, and constipation. Where the two agents are administered conjointly a much less quantity of chloral is necessary in order to produce sleep. These agents act much more favourably when administered simultaneously. Chloral causes sleep; morphine relieves pain; atropine prevents or lessens the depression in the respiration and cardiac movements caused by the other two, while it contributes to their cerebral effects.

These physiological studies are confirmed by therapeutical results. The combination of Chloral, Morphine and Atropine is adapted to these cases of insomnia caused by pain, or in which chloral or mor-

phine merely increases the cerebral excitement, as in hypochondria, puerperal mania, etc. This combination is also indicated in cases of fatty and irritable heart. When pain is to be relieved, chloral is not so serviceable as the combination with morphine and atropine."

Butyl-Chloral Hydrate is doubtless a hypnotic and it is decidedly less dangerous than Chloral Hydrate but its hypnotic effects are not to be compared with those of the latter drug. When introduced by Oscar Liebreich he thought it possessed all the advantages of Chloral Hydrate but it had little or none of its great drawbacks and he used it largely as a soporific. Subsequent use of the drug has not confirmed all the great qualities which were claimed for it on its introduction and it is now seldom used as a pure hypnotic. It is a much feebler hypnotic than Chloral Hydrate and produces less cardiac depression; although Liebreich said it did not interfere with the circulation or respiration, which statement however is hardly correct, for all authorities are agreed that it does depress the circulation although not in a

marked degree and on the few occasions that I have used it I have invariably found its depressant action quite distinct.

Later Liëbreich somewhat modified his views but maintained that its action on the heart in large doses was not dangerous and in animals that had been poisoned by it life could be restored even after respiration has stopped by resorting to artificial respiration, or in other words, that its effects were directed wholly to the respiratory and not to the cardio-inhibitory centre. Mering, however, demonstrated that its action on the heart was very similar to that of chloral, although not to so great a degree and a number of authorities now look on Butyl-Chloral as Chloral whose action as a cardiac depressant is much diluted.

Its great advantage is that it has a selective, anodyne, or anaesthetic action on the fifth pair of nerves and therefore it has great advantages where insomnia proceeds from any painful affection of these nerves and it is chiefly used on this account;

and as its success as a pure hypnotic has not been great or even marked it should not be used in routine treatment for insomnia but only where you have special indications for its use - by its action on the fifth nerve or else where other hypnotics have failed in simple insomnia.

Lastly there seems to be great uncertainty in regard to its dose. Liebreich has recommended as much as sixty grains as a soporific, whilst Ringer (41) says "I have given five and ten grain doses in a considerable number of cases, but never knew either dose to produce sleep or even drowsiness," and Yeo has found two grains sufficient. Whitla (42) recommends ten grains for the first dose and five grains every two hours for three or four more doses.

Some years ago I took the drug for the relief of neuralgia and on one or two occasions I took two doses of three grains each within half an hour of each other without producing the slightest drowsiness and therefore from my own experience I cannot agree with Yeo that two grains is sufficient but I am much

more inclined to think that fifteen grains should be given as a soporific.

Regarding the uncertainty of the dose and the various views which are held concerning it - that it is a dangerous and powerful drug on the one hand and that it has hardly any element of danger on the other - I think both may be attributable to one of two causes:- firstly, the possible impurity of the drug, either primarily or the result of decomposition from being kept some time , and secondarily, the manner in which it is administered, either in solution, when we should remember its insolubility, in water, or in pill. I think that if a fresh specimen were always used and that it were dissolved in glycerine and rectified spirits we should not have much divergence of opinion and I should strongly recommend that it should always be given in this manner.

There are no less than seven preparations or combinations of Chloral Hydrate with other bodies at the present time which are or have lately been

used as hypnotics in most of which the second substance has been combined to counter balance its depressant action, these are :- Hypnal, Ural, Chloramide, Chloralose, Somnal, Chloralimide and Chloralammonium.

Hypnal is a synthetic remedy which is a combination of Chloral Hydrate with Phenazone (Antipryine) which has been introduced so as to combine the hypnotic qualities of the one drug with the analgesic properties of the other. According to some chemists Chloral forms several compounds with Antipyrine, the chief of which are mono and di-chloralantipyrin and also an acetyl derivative of mono-chloralantipyrin. One of these has been found to possess well marked hypnotic properties and to that one (which it is I cannot say - as it seems to be a trade secret) the name Hypnal has been given. It occurs in the form of rhombic crystals, which are colourless and tasteless and are soluble in about six parts of water. It has only had a very limited use as far as I can find and it is therefore upon its trial; but should all that is

claimed for it prove to be true it will doubtless have a more extended use.

Prof. See (43) says it is superior to Chloral on account of the less depressing action it exerts on the heart and blood vessels; but that as a general soporific he does not consider it equal to Sulphonal. Dr Bardet (44), who has probably had the largest experience with the drug, thinks it is a very efficient hypnotic and analgesic, and that it is specially indicated in cases of sleeplessness - where it proves most effective - even if the insomnia is caused by pain or cough. He gave it altogether to twenty-two cases and found that fifteen grains caused sleep quite as easily as a fairly large dose of Chloral Hydrate, which clearly shows that it must possess properties quite independent of the constituent drugs; because the dose he used of Hypnal would only contain six grains of Chloral Hydrate which could hardly be said to produce much effect by itself.

As so little is known of the drug at present I think it is better to reserve any opinion I have

until I have given it a trial but it seems worthy of attention on account of its palatability and solubility.

Ural is also known under the names of Uralium and Chloral-urethane. It is produced by precipitating a solution of Urethane in Chloral by the addition of Hydrochloric Acid. It has a formula represented by $C_5H_8Cl_3NO_3$. It forms crystals which are insoluble in cold water but decomposed by boiling water. It is freely dissolved by alcohol and ether from which it can be precipitated by water.

This substance has been highly extolled by Gustavo Poppi of Bologna (45) to whom in fact we owe the name of Uralium. He concludes that it induces sleep more quickly and more certainly than any other known hypnotic and that it causes no alteration of blood pressure. It is claimed for it that the Urethane counteracts the action of Chloral on the heart.

Although Poppi has bestowed such praise on it, it has not been so received by all hands. It is very ^{dis}agreeable to take and causes nausea, vomiting,

and vertigo often. Again its action has been said by Dr Schmitt and others to be uncertain and I believe that it has been found to lower the blood pressure. The dose is from 15 to 40 grains.

Chloralamide. ($C_3H_4NO_2Cl_3$) is prepared by the interaction of Chloraldehyde (not Chloral Hydrate) and Formamide. $C Cl_3CHO + CHONH_2 = C Cl_3CH.OH.CONH_2$.

It occurs as lustreless, colourless, odourless crystals, having a slightly bitter taste. Its melting point is $111^\circ C$. and at a higher temperature it dissociates into its components. It is slowly soluble in 10 parts of cold water, or in $1\frac{1}{2}$ parts of 96% alcohol. It was used therapeutically I believe in the first instance by Prof. Von Mering, of Strassburg and has been recommended by Reichmann, Hagen, Hufler, and others, as a safe hypnotic in doses of from 15 to 40 grains.

It has also received recommendation at the hands of a number of British Practitioners. From these reports it seems to be a safe hypnotic, sleep coming on in less than one hour which lasts from six

to eight hours. It has also been stated by a number of authorities to cause no dilatation of the arterioles or fall of blood pressure and to have no depressant action on the heart and therefore suitable for administration in cases of heart disease and bronchial affections where chloral hydrate would be contra-indicated; but I think that this freedom from causing depression of the heart and circulation needs further confirmation for as I shall show directly all those who have reported on its action are not agreed on this. Dr. D. R. Paterson, of Cardiff, reports favourably on the whole concerning it for he says (50) that the result of his experience of it in fourteen cases of insomnia, including simple sleeplessness and that resulting from phthisis, heart diseases, typhoid fever etc., was satisfactory. The dose he used ranged from 30 to 45 grains dissolved in warm water. He says that on the whole its action was satisfactory, producing sleep of six to eight hours which was tranquil and unbroken and without any untoward effects. He gave it in a case of heart disease without influencing the

pulse. He also found it checked the profuse night-sweats of phthisis. But on the other hand insomnia and restlessness resulting from pain were little if at all influenced by the drug. And in one or two instances when he gave from 30 to 45 grains he found it followed by giddiness, nausea, staggering gait, etc. although not to an alarming extent. He found that sleep came on half an hour or an hour after giving it, which he looks upon as a disadvantage; but he said it was compensated by the almost entire absence of action of the drug on the circulation. It has no influence on the digestion and the appetite remains unimpaired. Von Mering recommended 45 grains as the dose but Dr. Patterson found 20 to 30 grains sufficient in the case of a woman, while 30 to 45 was usually quite sufficient for a man, and he stated that he considered Chloralamide a valuable addition to therapeutical remedies, especially in sleeplessness resulting from or co-existent with cardiac mischief, or other disease where the circulation is in any way affected.

Professor Leech (47) has also investigated this drug and he considers it a useful somnifacient generally. Dr Cope (48) has also found it to be a valuable hypnotic for the insane in doses of 25 to 35 grains to produce sleep in those suffering from melancholia and chronic mania and in doses of 40 to 50 grains in acute mania. We have therefore evidence on the one hand that this drug is a safe hypnotic which has little or no action on the pulse and it has also been stated not to have the unfortunate property of inducing a habit like its closely allied neighbour. I think that we should not come to too hasty a conclusion as regards its merits or demerits, for it can hardly be said to have established itself yet; for it has only been used to a comparatively limited extent up to the present and some openly state that it has the action of chloral only, and many found unpleasant actions following its use.

Dr. Malaceowsky says it produces sleep by diminishing the excitability of the brain and spinal cord and that it reduces the frequency of the pulsations of

the heart by acting upon the cardiac inhibitory centre and some physiologists, I believe it was Mairer and Bosc of Paris state that as the result of their physiological experiments they came to the conclusion that the actions of chloralamide and chloral hydrate were exactly similar if allowance was made for the less proportion of Chloral in the former and I believe that Dr. Schmitt came to the same conclusion from the result of his clinical observation; then again Pye Smith and Unfenbach (50) have observed unpleasant symptoms following its use, notably a desquamative dermatitis and depression. Genersich also, I believe, reported that he had observed some distinct depressant action on the pulse and we have the evidence of Dr. Patterson before quoted, that in one or two instances, when he was giving the full dose usually employed, found certain unpleasant effects produced.

I think that in the face of all this evidence that if we take a dispassionate view of the case the best we can say about Chloralamide is that it seems to be safer than Chloral Hydrate and should be

used as a hypnotic in its place until experience or a wider knowledge of the drug either proves it to be free from ill effects, or on the other hand, should direct us exactly as to its action.

In prescribing Chloralamide it is well to remember that either heat or the action of alkalies decompose it into Chloral hydrate, and ammonium formate and it should therefore never be ordered to be dissolved in warm water. It is best given in capsules, on account of its disagreeable taste or dissolved in some aromatic tincture.

Chloralose is the name given to a comparatively new drug by M. M. Hanriot and Ch. Richet, Paris, which is formed by heating anhydrous chloral and glucose together. It is represented by the formula $C_8H_{11}Cl_3O_6$. It occurs as white crystals, which have a bitter taste and are soluble in hot water but only sparingly so in cold (about 2 to $2\frac{1}{2}$ grains to the ounce). It has been stated that this drug possesses the remarkable contradictory properties of acting as a hypnotic whilst at the same time it increases the excitability of the

spinal cord.

The literature of this drug is very meagre and as it has only been before the profession four or five years at the most and been only little used during that time it can hardly be said that we know much about it as yet. It seems to be serviceable in cases of insomnia due to overwork or excitement or when the result or accompaniment of heart disease but it has little or no analgesic properties and is therefore of no use in insomnia caused by pain

Dr Landouzy (51) and Montard Martin have used it clinically for some time in cases of obstinate sleeplessness and have found it fulfil their expectations. They gave it in doses of from 3 to 10 grains.

Rossi also has used it in mental cases with success and F. G. Morrill (52) considers it safe in cases which are uncomplicated with hysteria or alcoholism. He states that it produces no habit, does not require progressive increase of dose and induces refreshing sleep without producing any disagreeable after effects. Should the few reports which

have come to hand of this drug prove well founded it undoubtedly has a brilliant future before it; but for the present at any rate we should reserve judgment upon it for so many of those chloral compounds when first introduced have received such high encomium on their introduction which have not always been deserved that one feels cautious before accepting laudatory notices of such compounds.

It is well to mark that this drug is very powerful and therefore requires to be used with great caution. The dose given is stated to be 2 to $7\frac{1}{2}$ grs., and this, as a rule, should not be exceeded. It is best administered in cachets because it is so sparingly soluble in cold water and it is doubtful whether or not it is decomposed by hot.

Somnal is another new hypnotic which was introduced by Herr Radlauer, a Berlin chemist, and is in reality Ethylated Chloral Urethane ($\text{C CL}_3\text{CH C}_2\text{H}_5\text{O. NHCO}_2\text{C}_2\text{H}_5.$) It consists of Chloral Hydrate and Urethane dissolved in alcohol and crystallised. It has a melting point of 42°C. and boils at $145^\circ\text{C. (in vacuo)}$. It seems to

have been very little used since its introduction. It has been stated to act similarly to Chloral Hydrate but to be free from its serious drawbacks and has chiefly been used in the hospitals of Berlin and Moscow. It is generally given in half-drachm doses dissolved in water with a little syrup and in such doses acts in about half an hour. The literature is so meagre concerning it that one knows little or nothing about it and I have never used it myself and so cannot say what its actions are, but as the other chloral compounds all seem to have depressing effects on the heart, until we know more of the drug I think we are justified in discarding it in favour of others.

Chloralammonium forms small acicular crystals which are soluble in cold water with decomposition. It melts at 62°C. to 64°C. In the solid state even it splits up and it is therefore not suitable for use as a hypnotic. From it is derived:-

Chloralimide which is formed by the action of heat.

The formula of this substance is $\text{C Cl}_3\text{CHNH}$ and it

should not be confounded with Chloralamide to which I have already drawn attention. The substance under consideration occurs as long crystalline needles, having neither colour, taste, nor odour. It melts at about 166°C. It is insoluble in water, but soluble in alcohol, but more so in ether, chloroform and fatty oils. It is a very stable compound and is said to be more active than its nearly allied neighbour orthographically. We know little about it, although Choay, I think, says it is superior to Chloral Hydrate and as it is at present upon its trial we cannot speak with any definiteness concerning it.

This, as far as I know, exhausts the long list of drugs which are compounds of Chloral; but as we are almost every day being brought in contact with new remedies it is possible that there are some others in the market of which I know nothing.

Urethane or Urethan. This substance is often designated as Ethyl-urethane. It is one of the large number of remedies which have been prepared of late years

synthetically. It is one of a series of compounds which may be regarded chemically as Esters of Carbaminic Acid. It is the Ethyl Ether of Carbaminic Acid and has the formula $\text{CO} \begin{cases} \text{NH}_2 \\ \text{OC}_2\text{H}_5 \end{cases}$ It occurs as colourless, tabular or columnar crystals, odourless, and with a sweetish nitre-like taste, readily soluble in water.

It was introduced in 1885 as a hypnotic. It was first discovered by Kobert and first used medically by Von Jacksch of Vienna who found it to be a hypnotic which was not followed by any objectionable after consequences. Prof. Schmiedeberg has used it largely and recommended it in doses of 15 to 30 grs. Drs. Otto & Koeing gave it as a sedative in mental diseases and Dr Riegel also extolled it as producing sleep resembling the physiological phenomenon. Its action seems to have been fairly well investigated. It produces refreshing sleep especially in cases where this has been hindered by conditions of cerebral excitement. It also has the great advantage of acting on the respiration as a stimulant and seems not to

affect reflex irritability. It therefore agrees with Morphine thus far but it has little or no anodyne properties. It does not reduce the circulation and is free from the injurious action of chloral hydrate on the mucous membrane of the stomach.

The literature on it is rather meagre; but I find Dr Clouston (53) considers it reliable and free from harm where insomnia is marked and intractable and Prof Leech and Dr Gordon also praise it, the former stating (54) that it is often most successful in simple insomnia in doses of 20 to 30 grains and of all the hypnotics it is the least likely to give rise to dizziness, headache, and other discomforts." whilst the latter says (55) that as a result of the administration in a considerable number of cases of insomnia it had a distinct hypnotic action when given in doses of from thirty to sixty grains. The sleep which it produced was always pleasant and the patients awoke without any confused feeling, never complained of headache, loss of appetite, nor any disagreeable sensation, but on the contrary, expressed gratitude for the refreshing sleep.

Of late years we have heard less and less of the drug, probably due to the fact that it is very uncertain in its action. Von Jacksch employed 7 to 8 grains and Dr Sanby I believe has found 2 grains sufficient, whereas others have used 20 to 30 grains and Whitla(56) states that in doses of 100 grains it often produces no appreciable effects.

The advantages of Urethane may be said to be its freedom from odour and unpleasant taste, it never disagrees with the stomach, its freedom from unpleasant bye-effects, its ready solubility and the ease with which it can be combined with correctives. On the other hand its great drawback is - its uncertainty of action, and as we have so many other more or less harmless hypnotics I feel certain that it will gradually fall out of use as it can hardly be said to have fulfilled the high expectations once formed of it; but it is always well to bear in mind that it can be given in safety as no ill effects have ever been known to follow its use and thus when we have tried other hypnotics and have failed, we might fall back on this one with confidence in this respect at least.

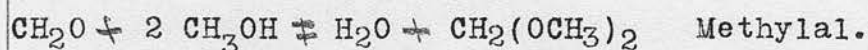
Hypnone or Acetophenone is related to Carbolic Acid and may be classified among mixed ketones. It is represented by the formula $C_6H_5CO.CH_3$ and is formed by the dry distillation of calcium acetate and calcium benzoate. The crude product contains about 6% of hypnone which is purified by repeated fractional distillation and solidified by cold. When pure it is a colourless oily liquid, having a peculiar odour and pungent taste. It is only slightly soluble in water, but readily mixable with alcohol, ether, and fatty oils.

It is an antiseptic but was introduced by Dujardin-Beaumetz as a hypnotic in 1885, after repeated experiments on lower animals. It was said to be superior to either chloral or paraldehyde, but it was found to reduce the blood pressure and the respiration was also affected and therefore great care was necessary in its use. Very little was reported concerning it for a year or so but since then very unfavourable remarks have been made concerning it in the medical papers. It was tried in the treatment of psychical diseases but was found to fail very often

and not only this but in those patients who were relieved by it, they very soon became habituated to its use. Still more recently according to Whitla (57) Hunt and Moebs have reported after exhaustive trials that the results are positively illusory in every case. Since this, little or nothing has been heard of the drug and we may safely state that its days are numbered as a hypnotic and we shall probably hear no more about it; as outside its doubtful effects it has a most disagreeable odour and taste, and furthermore it causes a great deal of gastric irritation, so much so, that the ordinary dose, 4 or 5 minims, even if given in capsules produces pain and vomiting.

Acetal has also been used as a hypnotic in doses of about two drachms; but it has a number of ^{the} objections of the foregoing drug including its uncertainty of action, disagreeable odour and taste, and so is unlikely to find a permanent place among the hypnotics.

Methylal, or Methylendimethylether is a mobile colourless liquid prepared by the interaction of methyl-alcohol, manganese di oxide and sulphuric acid, distillation of the product and purification by repeated fractional distillation. By this the methyl-alcohol is oxidised to form aldehyde and this reacting on undecomposed methyl-alcohol forms Methylal.



It has a penetrating ethereal odour and is soluble in water (one part to three) ether, and fatty oils. It is not altered by alkalies but is decomposed by strong sulphuric acid.

It was introduced by B. W. Richardson as a hypnotic; but has been very little used in this country. In doses of one to three drachms it causes sleep and seems to be very safe, although it has been observed to reduce arterial tension. It acts pretty certainly in ordinary cases of insomnia although Whitla (58) states that it very often fails but I think that this is due to the fact that in some instances at any rate it has been used in cases of al-

coholic mania, here I have found that it produces little or no effect at all; but if we exclude such cases I think we may look upon it as a reliable hypnotic. Whitla (59) has also recommended it to be used hypodermically but I think this is hardly justified by experience for it always produces severe pain locally and rarely can you get a patient to submit to hypodermic medication on a second occasion; the recollection of its first use being sufficient to prevent the patient undergoing a similar ordeal.

Its rather a pleasant odour and agreeable taste make it much preferable to either acetal or hyphne but as it is so expensive (costing eight shillings an ounce) it will never come into use as a routine drug.

Sulphonal, or to give it its more correct chemical title Diethylsulphonil-dimethyl-methane, is one of the most valuable synthetic hypnotics which modern chemistry has produced and which has been admitted to a place in the official materia medica of a number of

European countries, including our own.

It is prepared by the action of anhydrous mercaptan and anhydrous acetone in the presence of dry hydrochloric acid gas. The upper part of the liquid which separates is mercaptol and this is washed and oxidised by permanganate of potassium.

It has also been manufactured by the action of Ethyl chloride or bromide on sodium thiosulphate, conversion of the sodium, ethyl thiosulphate into ethyl mercaptan and acid sulphate of sodium by the action of water. As this conversion takes place in the presence of alcoholic hydrochloric acid solution with acetone, the ethyl mercaptan is condensed in statu nascendi to mercaptol which is then oxidised as before described.

We may chemically regard it as Methane(CH_4) in which the hydrogen atoms are replaced by methyl and diethyl-sulphon radicals and is represented by the formula $(\text{CH}_3)_2\text{C}(\text{SO}_2\text{C}_2\text{H}_5)_2$

It occurs as colourless, inodorous, nearly tasteless prismatic crystals melting at 125° to

126°C. It is soluble in about fifteen parts of boiling water and in about 450 of that fluid when cold. It is also soluble in cold rectified spirits and freely in boiling alcohol and in ether (about 1 in 135 at 15°C). It is a very stable body, being unaffected by acids, alkalies, or oxidising agents either in the cold or when warm.

This body was introduced by Professor Baummann (60) of Freiburg University and its action was investigated afterwards by Professor Kast (61) of the same University. It is the type of a pure hypnotic possessing no analgesic properties and in doses of fifteen to sixty grains it produces lengthened and refreshing sleep. From experiments on dogs it has been shown to influence the grey nervous matter of the brain and spinal cord. Shortly after it had been administered it produced some ataxic movements and signs as if the animal was intoxicated and from this it passed into a deep slumber. After awaking the movements seemed unsteady for a little while but this gradually passed off. There was no impair-

ment of appetite, nor was the heart or circulation in the least depressed nor were there any other unpleasant after effects noticed.

In man doses of 20 to 60 grains produce a feeling of sleepiness, or heaviness, or actual sleep. the sleep coming on in from $\frac{1}{2}$ hour to two hours after the administration and lasting from five to eight hours. On awaking, as a rule, no unpleasant effects are noticeable nor does the circulation or respiration become seriously depressed.

Since its introduction it has been used largely and almost all reports agree with my own experience that in cases of insomnia unaccompanied by pain it is the safest and best hypnotic which we at present possess producing no ill effects. Its great drawback is its insolubility and as it is so slowly absorbed from the alimentary canal - unless precaution be taken - sleep is not produced but a feeling of drowsiness only which may extend through the whole of the next day.

As the literature concerning this drug is

so extensive it hardly seems necessary to draw attention to any of the reports concerning it but as long ago as 1889 Lauder Brunton (62) in the Croonian Lectures stated that Sulphonal appeared to be one of the most effective of all the newly introduced hypnotics and that although it does not, like morphine, compel sleep, it induced sleep in a pleasant manner and has few disagreeable after effects and little or no danger.

It has also been found to be a useful hypnotic (63) in cases of insomnia, without organic disease, in cancer of the rectum, and cerebral meningitis and still further it has been given with success (64) in the sleeplessness of Bright's Disease, where narcotics were contra-indicated. It has also been employed in mania with success, also in locomotorataxy, and even in cases (65) of valvular heart disease. Dr Bottrich (66) found it to act like atropine in insomnia associated with phthisis especially in the earlier stages.

Dr Gordon (67) of Aberdeen University has

carefully studied the comparative values of Sulphonal and Chloralamide as hypnotics and says that in doses of 10 to 45 grains the former produced sleep lasting from six to nine hours. In a case of suicidal mania it was given over thirty times and always with good effect.

Again Dr C. Norman (68) has reported his experience of cases treated by him at the Richmond Asylum. He had records of twenty-two cases carefully noted. The patients suffered from Melancholia, puerperal mania, acute mania, delirium tremens, etc., and in only two cases were any bad effects noticed and in these other sedatives had not produced any effect. There was no gastric or intestinal disturbance, in fact in many cases, the appetite was improved and the sleep produced was natural, refreshing and undisturbed by dreams

No sulphonal habit has been found to be that produced and the only objection is a slight cumulative action has been observed.

It seems to be a perfectly harmless drug

for as far as I know only one fatal case (69) has been reported - although it has been given in very large doses. Its harmlessness has been demonstrated practically, on more than one occasion, a case being reported of a healthy man having taken 463 grains and this caused sleep which lasted 114 hours with a short interval and no deleterious effects were experienced. I see that Bresslauer and Joachim (71) state that they have found after long use it gives rise to vomiting and constipation, ataxia of the lower limbs with paralyzes and muscular spasms, anuria, ischuria, and haemato-porphyrinuria and in some cases it ends fatally; but they also add that they have never had bad results since they have made a rule never to give it more than three days in succession in doses not exceeding two grammes pro die and at the same time to regulate the bowels and kidneys. On the other hand Dr Chamberlain (72) records a case of insomnia with bladder and urinary trouble in which he used sulphon-al almost continuously for twenty-six months and no bad effects were noted, although the commencing dose

of 20 grains was never much reduced.

There seems to be some difference of opinion therefore as regards the possibility of chronic poisoning with this drug, and I would only add my own experience on this point, as I have used it largely. Since 1890 when I first heard of some ill effects said to have followed its prolonged use I determined to give it a thorough trial. Unfortunately I have not kept a record of every case in which I have used it; but I have no doubt that I have given it in 300 to 400 cases in all, in varying doses and for long periods together and in all manner of diseases. To show what a large trial I gave it I might mention that at one time I used to order from one to two ounces of it weekly to the many patients that came under my care at the Plymouth Public Dispensary and I have always found it reliable and safe; as although I have made repeated enquiries and took particular notice of the urine I was never able to detect the slightest sign of those symptoms which have been ascribed to its poisonous effects and it would require much stronger evidence than one or two isolated

cases to convince me at all events of any danger which should preclude its use. As some of these recorded cases are not absolutely free from suspicion that some of the symptoms which have been said to have been the result of the poisonous action of sulphonal are not those of some disease which had not been detected previous to the exhibition of the drug, and peculiarly enough the same symptoms have also been ascribed to the action of tetronal and trional - bodies closely allied to sulphonal chemically - where in the fatal cases, said to be caused by trional, at least Beyer has thrown considerable doubt - if he has not absolutely proved - that these symptoms have not always been due to the drug and to which I shall refer when I speak of these drugs.

So I think we may dismiss the subject of chronic poisoning with a notice to the effect that cases have been reported showing the possibility of such a condition but for the present at all events the evidence is neither sufficient nor conclusive enough for us to draw any conclusions as to whether a

such a condition is likely to occur nor in what particular class of cases it should be looked for.

No sulphonal habit has been found to be produced and from experience I know that we do require to increase its dose in long continued cases due possibly to a slight culminative action which has been said to be produced.

Lastly I would refer to its insolubility.

It has been the experience of all those who have tried this drug that if it be taken on going to bed it may take some hours before acting and secondly the patient then may feel drowsy almost all the next day, and so much so that some patients have found that it produced better effects the second night after taking it and many authorities have therefore recommended it to be taken only on alternate nights. Now I feel assured that these symptoms are due only to its insolubility and that if care be taken to make sure that it is in a state of solution at the time of ingestion the sleep will come on more rapidly and certainly the drowsy feeling the next day will not be of common

occurrence. I very well remember ~~a case~~ some two years ago where I was called in consultation to a case of insomnia and when I suggested that Sulphonal should be given in 20 grain doses, my brother Practitioner said it was of no use, as 15 grains had been given which produced no effect and as at that time I was experimenting with the drug and using it largely I was rather sceptical as to its not producing any effect and I still suggested that it should be again tried with certain precautions so as to make sure of its being in a state of solution at the time of giving it. It was dissolved in hot whisky and water and given just before retiring to rest with the result that the patient had a very good night and slept for eight hours and felt no effect the next day. Later the dose was reduced to 15 grains and the original dose given was found to act similarly. This was clearly a case of the drug not finding its way into the blood in sufficient quantity to produce any effect, being eliminated nearly as fast as it was absorbed. In the first instance I should mention the Sulphonal was

given in Tabloid form and swallowed with a little cold water.

Many authorities - on account of this deferred action - give it two or three hours before bed-time; some even giving it about 4 or 5 p.m. Whitla (73) gives it in fine powder made up as a sandwich between two ~~thin~~ pieces of thin bread and butter and he says that in this form it should be given three or four hours before bed-time.

When given as the powder simply or in Tabloid form no matter how long we give it before bed-time we find it does not act so certainly as when freely dissolved nor are we at all likely to find the drowsiness make its appearance the next day when it passes easily into the circulation.

My own experience has taught me always to give the drug in solution just before, say half an hour before, lying down. I usually order it to be given in hot milk or soup and with special directions that the fluid be very hot at the time the drug is introduced into it and that the patient or attendant

makes quite certain that it is wholly dissolved before drinking the mixture. On the other hand where I find my patient has been in the habit of taking a night-cap in the shape of alcohol in some form at night, I order the powder, generally 20 to 30 ^{grain} grains, or else 4 to 6 Tabloids, to be dissolved in the hot spirit and water, for sulphonal is so much more soluble in hot spirit that one is fairly certain of its being then perfectly dissolved. Should patients prefer not to have it, in one form or another, which is very seldom, I order it to be dissolved in boiling water, which is then allowed to cool until fit to be drunk when it is ^{to be} taken; for as a writer in the medical journals has pointed out it does not precipitate on cooling which is a point worthy of drawing special attention to, as it does away with the special disadvantage of this drug.

When given in one of the manners indicated I have invariably found it to be certain and fairly rapid in its action and furthermore I have not found that sleepiness often follows on the next day.

In conclusion I would say that it is the remedy par excellence in insomnia as a routine drug and that it can be used in a whole range of diseases where insomnia is present - in fact there are only four classes of cases in which I prefer other drugs; Firstly:- Where pain is present when of course opium takes a prominent place or chloral-hydrate or chloral-urethane, the latter two standing in a second place and separated by a long interval from opium.

Secondly:- In cases of insanity where it is bound to give way to Hyoscine or Paraldehyde, although Rabbas (74) has stated he has found it act when Paraldehyde failed.

Thirdly:- In sleeplessness due to lung affections, where I much prefer Amylene Hydrate as advocated by Scharschmitt (75) and Leech (76).

Lastly:- In cardiac affections, where I prefer Amylene Hydrate, paraldehyde, or urethane. In these last cases Sulphonal sometimes causes cyanosis or increased breathlessness - although Kast used it successfully in cardiac asthma.

Schmeyer² has found Sulphonal to be contra-indicated in cases where there is degeneration of the vessels and I myself in the only case that I can recollect in which I gave it in such a condition found that the anginal attacks were increased both in intensity and in number, so much so that I never give the drug in such states now as I am convinced that the other drugs mentioned are preferable.

Outside these classes of cases I invariably use Sulphonal because it is doubtless one of the safest hypnotics we possess and it produces a natural kind of sleep, it does not constipate like opium, and it has neither taste, nor odour, these last two properties having great weight as we find patients sometimes object to take drugs and most decidedly so if nauseous especially in the case of children; and then there has not been found a "habit" for this drug.

These properties are such that they are bound to command respect and indeed to them I think we can say that on account of them to a great extent do we owe the fact that Sulphonal is driving most of its newer rivals out of the field of therapeutics.

Amylene Hydrate is one of the eight possible alcohols with the general formula $C_5H_{12}O$. It is Tertiary Amyl Alcohol or Dimethylethyl-carbinol and is represented by the formula $(CH_3)_2 C_2H_5 COH$. It was in the first instance prepared by Wurtz and identified later by Osipoff and Flavitzky.

It is prepared by the action of Sulphuric acid upon Amylene at a low temperature, the amylene-sulphuric acid is then separated, diluted with ice-cold water, filtered and then neutralised with chalk or soda and distilled. The distillate is then freed from water by the action of potash and fractionated and the fraction which passes over between $100^{\circ}C$. and $102.5^{\circ}C$. being collected.

It occurs as a colourless, limpid, hygroscopic liquid, with a peculiar penetrating odour like ether, reminding one of peppermint and camphor. It has a specific gravity of .810. It dissolves in eight parts of pure water at $15^{\circ}C$. the solution being turbid when warmed. It is miscible in all proportions with alcohol, chloroform, and ether.

It was first used by Prof. T. Von Mering as a safe substitute for Chloral Hydrate especially in cases of nervous sleeplessness, being without any action on the respiration or heart. In very large doses it has been found to paralyse the medulla oblongata.

It is usually given in doses of 30 to 60 minims , but no bad effects have been found to follow doses of 2 drachms. It seems to act like chloral. There is no preliminary stage of excitement and sleep comes on very rapidly, generally in a few minutes, which seems to be a perfectly natural refreshing slumber. It therefore seems to be another pure hypnotic. It very seldom fails in its action and is therefore very reliable even in those cases occurring in patients accustomed to narcotics and there have been found no ill effects following its use and moreover it may be safely given to children. It has been stated in some cases to be anodyne but ~~also~~ this requires confirmation. After the remedy has been given some time it appears to have the drawback of not being

easily borne, although this is not the case in all instances. It is best administered with Claret or some weak wine, or the following is a very useful combination.

Amylene Hydrate. M. 100.

Extr. Glycyrrh.liq. 3 ij.

Aq. Destill. ad. 3 iij.

Half to be taken in the evening before going to rest.

This is a useful combination as the unpleasant taste is to a great extent masked and the quantity of liquid is sufficient to completely dissolve the amylene hydrate. This last item is important as otherwise if a draught as ordered above contain not sufficient vehicle the amylene hydrate would float on the top and instead of getting the proper dose one might produce unpleasant effects, so that some (78) lay down a rule that it should only be dispensed in one dose. Some prefer capsules as a mode of administration but the above is far preferable and is the manner in which I prescribe it.

Many have recorded their opinions of the drug and all seem to be agreed as to its uses and

effect. Amongst others, besides V.Mehring, Avellis, Gurtler, Mayer, Riegel, Rosenbach and Wildermuth have used it with satisfactory results.

Von Ulcering of Strasburg (79) has given it in sixty cases and in all except four the effect was more or less complete and after a dose of from 3 to 5 grammes refreshing sleep was produced. Teiser (80)(Fortsch d. Med.) as a result of special investigations has found that Chloral Hydrate increases considerably the decomposition of albuminous matter of the body. Amylene hydrate has the opposite effect. He concludes that in all the diseases in which the use of a hypnotic is likely to be required for a long while, and especially in those diseases where there is great waste of Nitrogenous matter, Amylene Hydrate is to be preferred. It has the advantage over Sulphonal and paraldehyde of a quicker and profounder action and as regards hypnotic potency Leech (81) places it between sulphonal and paraldehyde. Others place it between chloral and paraldehyde. About 15 grains of Chloral hydrate are equivalent to 30 minims of

Amylene hydrate and 45 minims of paraldehyde.

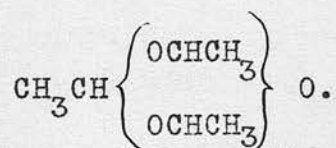
We may sum up this drug by saying it stands next to Chloral hydrate in point of certainty of action although Gurtler asserts it is as potent as the older drug, but it has no depressant action on the circulation or respiration, that it cannot be relied upon in sleeplessness accompanied by or due to pain.

My own experience has been that it is preferable to sulphonal in the insomnia of cardiac and lung affections and is specially indicated in these cases, but that on account of its unpleasant taste and expensiveness, Sulphonal is preferable to it as a routine drug.

(82)

I should mention that Dr Surzycki[^] prefers Sulphonal to Amylene even in cases associated with phthisis and cardiac affections.

Paraldehyde or Elaldehyde is the product of the condensation of three molecules of ordinary ethyl aldehyde. Aldehyde is represented by the formula C_2H_4O and Paraldehyde by $(C_2H_4O)_3$ or thus



Ordinary aldehyde is treated at a medium temperature with small quantities of hydrochloric acid, carbon oxychloride, sulphurous anhydride (sulphuric acid causes explosive ebullition) or Zinc.Chloride. The temperature of the liquid gradually rises and we get almost complete conversion into paraldehyde. It is then purified by repeatedly freezing out and rectifying.

It occurs as a clear colourless liquid, having a peculiar characteristic ethereal odour and a burning and afterwards cooling taste. It has a specific gravity of 0.998. Boiling point 255.2°F. (124°C.) It is said in the B.P. addendum 1890 to congeal to a clear crystalline mass as 50°F. (10°C.) but I think it should be pointed out that even pure paraldehyde may be cooled much below 10°C. without crystallising unless it be stirred whilst the temperature is falling and it would be better if such facts were made known in our new pharmacopoeia as otherwise it might cause some misconception regarding the drug.

It is miscible in all proportions with rectified spirit or ether. One part is soluble in 10 of water at 60°F and forms a neutral solution. If added to water in excess of the quantity which the water will take up it forms an emulsion.

It should also be remembered that paraldehyde is readily convertible into acetic acid by oxidation and even by the action of the atmospheric oxygen and therefore it will not often long be absolutely neutral. It is important therefore if possible to use only freshly prepared paraldehyde or that which is kept in well stoppered bottles.

It was first investigated by Cervello(83) in 1882 and was introduced into materia medica about the next year as a hypnotic and made a reputation so widespread that it was adopted officially in both the ^{British} and German Pharmacopoeias. When introduced into the stomach it is rapidly absorbed and produces hypnotic effects, in the first place giving rise to a condition of slight intoxication which is followed by a deep sleep which lasts for some hours and on awakening

there are no unpleasant after ill effects except a disagreeable odour of the breath caused by the drug being excreted by the lungs.

Physiologically its action is somewhat similar to Chloral hydrate excepting its effects upon the circulatory system. It stimulates the respiratory centres and strengthens the heart's action while diminishing its frequency. There is some doubt as to whether it affects blood pressure, some stating that it dilates the arterioles, whilst others state that there is a negative effect. It has a well marked action on the kidneys, greatly increasing the flow of urine. On the skin it has no action at all. The drug is said not to give rise to any digestive disturbance but I cannot say that is absolutely true as we often get eructations following its employment with sometimes nausea and vomiting. The great advantage is that it can be given for even months at a time without as a rule increasing the dose (84) A habit has been observed to follow its use and it has been said that a state allied to chronic alcoholism has foll-

owed its employment but when one remembers its unpleasant odour which it imparts to the breath one feels that the chances of using it habitually are rather remote.

It has been found serviceable in almost every form of insomnia, where pain is absent, and especially in mania, melancholia, and nervous affections, as well as that accompanying acute bronchial catarrh, lobar pneumonia and heart diseases and as regards the latter cases it is the most reliable hypnotic we possess. Some state that it is inferior to Sulphonal in lung affections but as already stated I think amylene hydrate the best drug in this class of cases.

In insanity Paraldehyde has undoubtedly given the best results that have been obtained so far, and here it has steadily but surely pressed its rival sulphonal out of the field which is chiefly attributable to the fact that unpleasant nervous symptoms have followed when the latter drug has been given for some time in much larger doses than those usually adminis-

tered and this has deterred physicians from pressing it as they naturally prefer the newer seemingly harmless liquid. The dose usually given is from 30 to 60 mins., but this limit may be far overreached without danger, it may be given up to 4 or 6 drachms - thus Clouston records a case where he gave it in doses of 4 drachms for a fortnight without any ill effect.

Its pungent taste can be disguised by giving it with tincture of orange or some bitter tonic or it may be given with some spirit such as brandy.

Paraldehyde has been used hypodermically in doses of 30 to 60 mins., but this method has not been received very favourably as it is so rapidly absorbed by the stomach that it possesses little if any advantage. Some recommend it to be given in capsules whilst others have used suppositories to get over the objectionable taste but in regard to the former one finds that the patients complain of the sense of heat produced in the stomach when the capsules give way and the latter also seems to be objectionable for evident reasons and so by the stomach

combined with some flavouring substance seems to be the best method to give it; indeed I rarely have found much inconvenience to arise when so given. The two great classes of cases that Paraldehyde then seems to occupy the premier position are those of mental cases and in heart disease.

Somniferin is a new hypnotic and narcotic, which has been introduced by Bombelon. It is a morphine ether which exists in fine transparent crystals. It is said to closely resemble morphine in its actions, but not to produce headache, itching, malaise or constipation. Its dose is somewhat smaller than morphine. At present we know little or nothing about the drug beyond what I have stated ^{and} ~~at~~ so one is not in a position to give any opinion as to its merits or demerits.

Trimethyl-Carbinol is a tertiary alcohol of a liquid oleaginous character. It acts as a powerful cerebral sedative and although a few experimenters have used the drug its therapeutic actions have not been

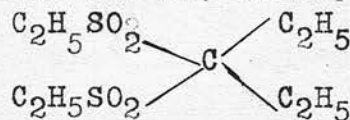
fully or clearly worked out. It has been given in 10 mins.doses in delirium tremens and in mental diseases.

Dimethyl-Carbinol has been found to be more active in every way than the former, although it possesses similar properties and it is possible that this latter drug will find a place soon in therapeutics as it has properties, which, if proved to be confirmed by experience, will place it in the front rank but one can do no more than surmise at present.

Tetronal & Trional. I have grouped these two bodies together because they are generally spoken of together and compared but as I shall show immediately the former does not seem to be as active as a sleep producer or in quieting mental cases, so that it will probably fall into disuse as its nearly allied neighbour (Trional) is supplanting it and seems to be the more generally adopted body of the two.

Tetronal is closely allied chemically

to Sulphonal and differs from it in the substitution of two ethyl for two methyl groups and it is therefore diethylsulphon -diethylmethane and may be represented by the following formula

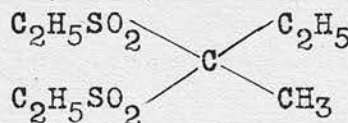


The name of course as in the case of Tri-onal has reference to the number of ethyl groups present. It occurs in lustrous, tabular, crystals or plates, which melt at 83°C. It is readily soluble in alcohol and fairly so in ether. In water it dissolves in 450 parts of cold water (the same as sulphonal). It has a bitter camphoraceous taste. As regards its action, all those who have used these two bodies have recorded their opinions that Tetronal is much inferior and indeed as pointed out by Bresslauer & Joachim (85) to Sulphonal as it possesses all the disadvantages of the latter without having its power and they also state that it is really more of a sedative than a hypnotic. One need not go over the literature of this drug as almost every authority without exception declares it to be inferior to

Trional and most relegating it to a place far below Sulphonal.

Trional differs from Sulphonal only in the substitution of an ethyl for a methyl group and its systematic name therefore is diethylsulphormethylethylmethane .

It is represented by the formula

$$\begin{array}{c} \text{C}_2\text{H}_5\text{SO}_2 \\ \text{C}_2\text{H}_5\text{SO}_2 \end{array} \begin{array}{c} \diagdown \\ \diagup \end{array} \text{C} \begin{array}{c} \diagup \\ \diagdown \end{array} \begin{array}{c} \text{C}_2\text{H}_5 \\ \text{CH}_3 \end{array}$$


It forms lustrous tabular crystals which melt at 76°C. It has a bitter taste. It is readily soluble in alcohol and ether but requires 320 parts of cold water for its solution, and is therefore slightly more soluble than sulphonal.

This drug has been experimented with by several observers and from all the reports it seems to be a powerful and safe hypnotic and it was stated by Schultze to be more reliable than either Sulphonal or Tetronal. When introduced it was expected, from experiments performed on living animals to be more powerful than Sulphonal, but Barth, Rumpal and others found that although indicated in certain nervous diseases where Sulphonal did not answer the dose had to

be quite as large (60 grains daily).

The literature of Trional since its introduction has been very extensive, although not so great as that of Sulphonal in the same period, this latter possibly being due to the fact that the drug gave such uniformly good results that there was little new for later observers to remark concerning it. It is true that in regard to certain details the results published by some in the earlier cases were in direct antagonism to those of others, but this was because the cases were then so few, that the element of chance and various qualifying circumstances were ignored so that false deductions were made from the premises. Just at this time also, several cases of poisoning were published and it was thought these cases would rapidly increase in number but such has not been the case for up to the present at all events, only six cases have been recorded and to which I will refer later.

Of the many who have used this drug largely and reported on its advantages I will only refer to

a few. Dr Boudeau (86) gave the record of its hypnotic effects in 30 cases of ordinary diseases. He used it in doses of from 1 to 4 grammes and found the weaker doses (1 to 2 grammes) particularly produce the weaker effect, whilst the stronger (2 to 4 grammes) had a sedative action in cases of irritation. He found sleep came on in about three quarters of an hour and lasted on an average for seven hours. It was quiet although easily disturbed but quickly renewed again. It was successful even in cases due to pain. In four of the cases it seemed to cause nightmare and in other four cases there was passing disturbance on waking but he never found any serious symptoms followed its use. The only case in which it failed was in a woman suffering from cardiac asystolia. He says it is a pure hypnotic and in therapeutic doses it has no effect on the circulatory, respiratory, or digestive apparatus, while it has little or no action on the temperature or secretions.

Dr Moncorvo (87) of Rio de Janeiro has observed its effects in children - in the first in-

stance in the insomnia of neurotics and found it to be so prompt and sure and at the same time harmless that he proceeded to give it to cases of exanthemata, particularly measles, scarlatina, and small-pox, he also gave it in cases of malaria and in all these it invariably succeeded in doses of 20 to 25 centigrammes. It was also successful in subduing cerebral excitement in pernicious malaria and in two cases of tubercular meningitis. In a case of right hemiplegia - due probably to cerebral hemiatrophy - in a girl aged three years, he used it daily in doses of 50 centigrammes for several weeks and produced a good effect without any disagreeable symptoms, and furthermore he found it serviceable in the insomnia of acute or sub-acute tuberculosis in young subjects and in painful diseases, such as Neuralgia and diseased bone. In all the cases it was well borne and had no disagreeable effect on respiration, circulation, or cerebral activity. He sums up its action by stating that of all the substances possessing hypnotic effects which he has tried, he has found none speedier or

more certain than Trional and that it is better borne by them than any other narcotic. It also has a sedative action on the brain which renders it useful in nervous or psychological excitement dependent on intoxications or lesions of the encephalon or its coverings. Spitzer (88), reporting on a great number of cases in Drasche's clinic in Vienna, said that it was given in doses of 1 to 2 grammes in the early morning after sleepless nights and finds that it is not only a hypnotic in psychoses, but that it acts equally well in lung (especially phthisis) and heart cases, and that it induced sleep quickly which continued as a rule during the following night - although some patients remained stupid with sleep even the whole of the next day - but the sleep resembled that of a normal person. He observed no bad effects on the circulation or respiration in any case but in isolated cases there was retching on waking which he attributes to idiosyncrasies, and the results he obtained were excellent even in the insomnia of neuralgia, etc., and in cancer and he says the effects resemble morphine more than those of any other hypnotic.

S. Wolfe (89) has found it superior in promptness, ease in administration and absence of bad or disagreeable after-effects to most if not all of the hypnotics. He says it acted almost the same whether given in a warm vehicle or as a dry powder or in capsules, sleep coming on within an hour as a rule. The dose he advises is 15 grains, although he thinks 10 grains often would be quite sufficient and he would lay it down as a rule that it is better not to give more than the first dose until the susceptibility of the patient had been first tried.

Regarding the poisonous effects of this drug it is well that I should offer a few remarks.

Bresslauer and Joachim (90) say that Trional as well as Sulphonal after long use produces symptoms of poisoning, which, in the latter case at all events, as already stated, have been unable to confirm and indeed my experience has been directly opposed to such a condition for in the many hundreds of cases in which I have employed it I have never had what one could call a case of poisoning by the drug.

As far as Trional is concerned the symptoms which are attributed to its poisonous action and which have been stated to have been observed at one time or another are dullness, giddiness, headache, anorexia, obstinate constipation, ataxia of the lower extremities and sometimes oliguria and strangury. These transitional cases lead up to the more marked ones of chronic poisoning which are distinguished by anuria, ischuria, and haematoporphyrinuria, hyperacidity of the urine and death. Now we should remember that although Trional has been given so frequently in the last five years, only six cases of what has been called poisoning have been reported, as far as I am aware. They are the cases of E. Shultze (91), Collatz (92), Hecker (93), Herting (94), Reinicke (95 & Berger (96).

The case of Collatz was one of acute poisoning caused by a person taking 8 grammes of Trional with suicidal intent and so need not detain us - as it only shows the possibility (as the patient did not die) of fatal acute poisoning.

Ernst Beyer (97), referring to these cases, thinks that Hecker's case is in reality the only one of true chronic poisoning and is the only one he will recognise as such and ^{here} there was no haematoporphyrin in the urine and the patient recovered. He says it is easily explained by the fact that as much as $1\frac{1}{2}$ grammes was given to a woman on 36 consecutive evenings ~~to a woman~~, which unless there is a special indication, is what he considers a decided mistake for he laid it down in a lecture (97) in June 1893 as a fact that women required .5 to 1 gramme less than men, and that in women unpleasant after effects were produced by doses that would only just be sufficient to operate in the case of men and that if in this case the dose had been regulated according to the individuality of the patient and with the precautions laid down by Goldman (98) it would have been avoided.

In regard to Herting's case - he points out that although the toxic symptoms followed immediately after the employment of Trional the patient had been taking Sulphonal first for a long period, and afterwards

Tetronal, and laterly Trional and Sulphonal together, and then a two gramme dose of Trional a week later when the poisoning occurred and so he says the haematoporphyrinuria may just as well be attributed to the Sulphonal and as we are not acquainted with the result of the post mortem examination, it is doubtful whether death was due solely to the poisoning.

The cases of Reinicke & Schultze he does not consider due to Trional poisoning at all, but to disease of the abdominal organs. He quotes a case of cerebral haemorrhage in which haematoporphyrinuria was present and where neither Sulphonal nor Trional had been given and he thinks that the haematoporphyrin in this case was due to intestinal disease, although he is not sure whether this substance passed through a recto-vaginal fistula directly into the urine. Haematoporphyrin has been found in the urine not only after diseases of the liver but also of other haematopoietic organs as mentioned by Loja (99) & Garrod (100). Then in one of his cases treated with Trional on account of insomnia, the urine became brown in colour,

but the presence of urobilin in large amount accounted for it and from these facts and others that he adduces he thinks Reinicke's a case of acute intestinal disorder (dysentery?) and that of Schultze a possible ulcer in the intestines or perhaps carcinoma of the liver and that he might go as far as to maintain that the presence in the urine of haematoporphyrin in these cases, which was absent in the undoubted cases of Collatz and Hecker, as well as in dogs poisoned by Trional by Bakofen (101) argues against Trional poisoning.

Lastly in the case of Berger, as the patient was a victim of the morphia habit and it was not known how much Morphia and Trional he took - he says it is of no practical value - as an abnormally large quantity of Trional was taken.

Beyer maintains that Trional should only be given in a single evening dose, and that a smaller quantity is efficient in women than in men, and that after a very extensive experience extending over three years, both in the Psychiatric Clinic and in

the Hospital for General Nervous Diseases at Strassburg, he says it is one of the best, if not the best, of hypnotic drugs, and that unpleasant results can easily be avoided with care and that seldom more than two grammes and never more than three grammes should be given. He recommends it to be given in the form of powder in a large cupful of warm milk, soup, tea, etc., shortly before bed-time and that during continued use of it it is advisable to administer alkaline mineral waters (Seltzer, Apollinaris) or if constipation exists to employ remedies which tend to increase peristalsis and secretion so that absorption of unabsorbed Trional may not take place.

Scognamiglio (102) finds Trional effective in nervous affections and he endorses Spitzer's views as to its utility in pulmonary affections, and in diseases accompanied with pain, such as neuralgia and tabes dorsalis. He finds it has no bad effect on either the circulatory, respiratory, or digestive systems. He has also made a series of experiments with it on dogs and rabbits and special observations on the urine of persons taking it in reference to its effects upon the kidneys.

As regards the animals, although daily examinations of the urine was made no haematoporphyrin was observed (the dose for dogs being .5 to 1 grm. and for rabbits .1 grm. to .5 grm. per diem). The kidneys also of the two dogs which were dying during the experiments were carefully examined microscopically and hyperaemia only was found in each case and on the other hand the dose in dogs was greatly increased (3 grm per diem) till on the third day the urine was blood coloured and contained haematoporphyrin.

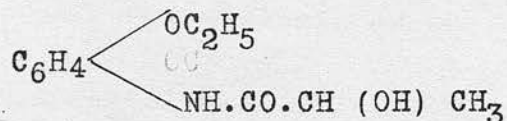
In the case of the patients, most careful examination failed to discover haematoporphyrin and as a result of his clinical and experimental observations he came to the conclusion that Trional was a safe and profound hypnotic when given in doses of 1 to 2 grms. per diem, and that it is superior to Sulphonal, Chloral hydrate, and Morphine, and that the production of haematoporphyrinuria was greatly exaggerated.

In taking a survey of the evidence produced by those who have used this drug largely (as I cannot speak with any authority myself, as I have not

used it sufficiently often to arrive at any definite conclusion) there is no doubt that it is a powerful hypnotic and that acute poisoning might result from a large dose, and secondly, that chronic poisoning is a possible danger that should always be kept in view but that such a condition is hardly likely to manifest itself if care and ordinary precaution be taken, and lastly, that we should always begin with a small dose unless we know the susceptibility of our patient. Whether Trional should take a place before Sulphonal or not in cases of simple chronic insomnia is a moot point; but as far as I am personally concerned I should unhesitatingly give my preference to the latter drug not only on account of my much greater knowledge, of it, but also for the fact that I consider that haematoporphyrinuria is a very remote possibility with its long continued use, although some authorities have formed an opinion that it is just as likely to occur in the one case as the other.

Lactophenin is a new derivative from Phenetidan

containing a lactic acid residue in place of the acetic acid one and it is therefore chemically lactyl-para-phenetidin and may be represented by the formula



It occurs as a white crystalline powder,, odourless and tasteless, having a melting point of 111.5° to 118°C. and soluble in about 330 parts of water. It is broken up into its component parts - lactic acid and paraphenetidin - by the action of either acids or alkalis. It is chiefly eliminated by the urine, giving a burgundy red colour by means of perchloride of iron.

It was first investigated by Schmiedeberg who found it to have an antipyretic effect, like the members of the antipyrine & phenacetin groups, quickly reducing the temperature, if it be raised, but at the same time producing a state of hypnosis far higher than those other drugs of this group and it also greatly reduces sensitiveness to painful impressions. Sensation and voluntary movements may

be completely abolished and reflex excitability nearly done away with by it, although there is no perceptible decrease of respiration or of the heart's action - in fact the narcosis is very similar to that produced by urethane.

Von Jaksch (103) has treated 18 cases of typhoid fever with it and 33 other cases and he has found it to have distinct sedative effects, besides its antipyretic action, and he has not noticed any injurious after effects, although he made more than a thousand separate and observations and gave it in cases with grave kidney mischief and in others with hypostatic pneumonia.

Jaquet (104) has also used it in 42 cases and has found no disagreeable after-effects, such as collapse or dyspnoea. He says its great advantage is the soothing hypnotic effect occurring with antipyresis. He relates a case of erysipelas of the face with a temperature of 104°F., where the man was so delirious that he had to be taken to the cell and where two persons could not hold him. He gave him

107.

the patient
3 grammes of the drug and ~~he~~ calmed down in a few hours so that he could sleep and on awaking he continued to be delirious but remained quietly in bed, and so by repeated doses of Lactophenin ~~he~~ kept him in a state of semi-somnolence until the delirium subsided.

Landowski (105) has also experimented with it and finds its strong antipyretic action is accompanied with a soothing and soporific effect.

Still later Carl Steinberg (106) has found it possessed of antipyretic, analgesic, and hypnotic actions and that there were no special after effects. The patients never suffered from headache, never felt faint, giddy, nor suffered in any such way - the pulse becoming slower but fuller. In respect to its special hypnotic action which I wish particularly to deal with, he repeatedly observed that it had a remarkable effect on the brain and on no occasion did he find the powder fail when he used it for this action. He mentions a case of tuberculosis where the patient was so delirious and violent that he considered the

advisability of transferring him to the psychiatric section, but by way of a trial he gave him 3 grms in 1 grm doses, without any appreciable effect the first day, and so he repeated it again the next day, when the patient fell into a deep sleep which continued the whole night and all the following day. In the further course of the disease he found that if necessary 1 grm was sufficient to produce sleep. He tried it in numerous other cases to produce sleep but there found that large doses (up to 3 grms.) were generally required. In four of his cases he found it very efficacious in causing delirium to subside and to quiet the patient completely.

Many others have tried the drug and all are agreed as to its hypnotic effect and although I am only just experimenting with it I am able to confirm their views on this point but so far I have had no ill after-effects. I think we may fairly class this among the list of the newer hypnotics as it certainly has a decided hypnotic action, quite distinct from its other actions. It is given in single doses of 8 to

15 grains, or in all from 60 to 90 grains daily in the form of powder, and although comparatively insoluble in water it is quickly absorbed in the stomach and therefore no special precautions are necessary to ensure its solution. It seems to be specially indicated in cases of insomnia dependent upon or accompanied with pyrexia and also in that due to neuralgia and kindred painful affections.

Piscidia Erythrina (Jamaica Dogwood) was introduced by Hamilton (107) of this town as a substitute for opium. It was first mentioned by Dr Barham of Jamaica in his Hortus Americanus in 1794 as a refrigerent wash. The root bark has long been used for taking fish in some of the larger rivers, where they throw a certain quantity into them with the certainty of stupifying a great number. It has also been probably known for a long time to medical men as a powerful narcotic but it seems up to a few years ago to have been little used by them.

(108)
Scott¹ was one of the first to test its

action who in conjunction with M'Garth, used it as a sedative and narcotic in certain cases in a lunatic asylum where they failed with opium and morphia. They used a tincture (1 oz. in 4 of rectified spirit) in doses of one drachm and they found the effect remarkable, as sleep was often soon produced, although previously the other narcotics in full doses gave negative results and from their reports it appears to possess special and hypnotic actions in certain classes of lunatics. From this time onwards, notices of its good hypnotic effects have appeared from time to time in the various medical and therapeutical journals, so that altogether I can trace no less than 80 cases where it has been used and from these I gather that in moderate doses it causes sleep which is not followed by after ill effects as seen in opium and morphia. It has no dangerous action on the heart nor any energetic action on the respiratory centre. It does not paralyse motor nerves like atropia, nor does it paralyse the chorda tympani nor arrest the action of the sudoriferous glands in fact it causes diaphor-

esis and salivation. It does not paralyse the vagus and it only slightly elevates arterial tension - but it does dilate the pupil. Except in this last respect its action is closely allied to morphine - it produces, sleep, heightened excitability, spinal convulsions, general paralysis and stimulation of the vaso-motor centre. It relieves pain and sometimes acts as a specific in neuralgia, and although its anodyne action seems to be inferior to opium yet it has heightened hypnotic power. It also relieves cough and spasm without affecting the centres like opium. In cases of insomnia even if associated with (109) asthma or chronic bronchial irritation, or (110) Cirrhotic Bright's Disease, or in (111) sleeplessness of the insane or in phthisis, it seems to be equally efficacious and it also seems to have the great advantage over opium in that a habit does not seem to be produced, and should this latter case turn out on a much wider investigation to be correct it will doubtless to a great extent replace that drug; but I do not think that it will ever have such a lasting reputa-

tation as opium nor do I think it will altogether replace it as some boldly declare.

The tincture, as I mentioned, was used in the first instance; but now the fluid extract (1 oz to 1 oz.) in doses of from one half to two drachms is usually employed, as it is the most reliable preparation.

Whatever preparation be used it should always be commenced with care as it seems to act differently on different people and toxic symptoms have followed the usual dose. Moore (112) relates a case where he gave half a teaspoonful to his mother for relief of neuralgia. This being rejected he repeated the dose and in about twenty minutes alarming symptoms manifested themselves which lasted with more or less severity for six hours but recovery ultimately took place. It has been pointed out that this case shows more particularly the idiosyncrasy of individuals to the action of narcotic drugs than a study of the toxic effects of this drug in particular for very much larger doses have been given with no apparent effect what-

ever.

Piscidin is the active principle and is the resinous body - which crystallises from alcohol in colourless prisms which melt at 192°C. They are insoluble in water, but slightly so in alcohol and ether and freely so in chloroform and benzol. Other resinous bodies have been separated but how far they affect the therapeutic action of the drug is not known and little also is known of piscidin as clinical reports of its action have not been forthcoming so far, and we must await these before it is possible to form any definite conclusion as to the exact part it plays in the effects of the drug.

It is difficult at the present time to say exactly what place Jamaica Dogwood will occupy in modern therapeutics but I think it at least deserves a trial in those cases of chronic insomnia where we should be inclined to give opium but where that drug is not particularly called for.

Boldea Fragrans or Penmus Boldus is a drug from whose leaves a liquid extract and tincture are prepared which is used in South America as a tonic especially in hepatic torpor and in gonorrhoea and chronic catarrh of the bladder. It has also been used as a substitute for quinine. From the leaves Boldin or Boldo-glucine - a glucoside - has been isolated. This has been used by Juranville as a hypnotic in doses of one drachm, given in capsules. It is said to produce refreshing sleep without any evil after effects and has been recommended in the insomnia of mania; but its action has never been thoroughly investigated nor has the substance been given a proper practical trial and so we know very little about it.

Acetanilide & Phenazone have both been credited with distinct hypnotic effects; but in these cases where sleep has followed their use it is due in all probability to their analgesic action as sleep would naturally follow the relief of pain.

I have not referred to Chloroform or Ether as hypnotic agents nor to those other drugs such as Methylene Bichloride which are closely allied to them in their actions, as they can only be of benefit in certain severe cases of insomnia which have resisted the powers of other hypnotics (a very rare condition) and of course their action can only be kept up for a comparatively limited period.

Other remedies such as Lettuce, Camphor, Musk, etc., have been used from time to time as hypnotics; but they are of no avail when the other drugs fail and they are so very uncertain in their action or so feebly hypnotic that they need not be given more than a passing reference.

Electricity & Massage may be successful in some cases and Digitalis helps sleeplessness by improving the tone of the arteries of the cerebrum.

Hypnotism has been tried successfully in some of those inveterated cases which have resisted all other

agencies and therefore it deserves a place in this text and it may come to occupy a very prominent place in such remedies but so much has been said on both sides - as to whether this mysterious agent should be tried or not - that it would take a larger notice than what I have given to all the other hypnotics taken together to discuss fully and adequately the arguments advanced so that I would prefer to leave the matter with the above simple statement.

In conclusion I would for a moment allude to those drugs which stand out prominently in the foregoing list, although I feel I need not refer to them at any length as I have brought into prominence their most marked characteristics and especially their advantages and disadvantages. In selecting a hypnotic for a particular case we are usually guided by three conditions:- 1st. Is it a case of simple insomnia? 2nd. Is it due to or associated with mental disease? 3rd. Is it due to or associated with some pronounced changes in one or more organs?

In the first class of cases Opium and Chloral & its compounds are certainly not called for and out of place. The bromides in most cases are very efficacious but, as already pointed out, they fail in some cases. Urethane, although safe, has the disadvantage of uncertainty of action and the shortness of the duration of sleep caused by it and the ease by which patients are aroused. Paraldehyde is nauseous, and Amylene Hydrate, besides being very expensive, also disagrees with many. Sulphonal & Trional are the most conspicuous members in these cases and which of the two is the better is hard to say - some preferring the one and some the other - but as far as I am concerned I have favoured the first named probably because it was the first that came under my notice.

In the second class two drugs seem to occupy places far in front of any others. I refer to Paraldehyde & Hyoscine, both of which have their advocates. Paraldehyde seems to me to be better as a routine drug in such cases, reserving Hyoscine for these violent outbursts of maniacal excitement.

Sulphonal has been praised by some in single large doses but I do not think it deserves the place allocated to it in such diseases.

In the last class, it depends greatly as to what organs or organs are affected. If pain be present, opium and morphia are doubtless of great value when indicated and next to it comes chloral or some of its compounds & urethane may possibly be serviceable, Butyl Chloral taking the place of Chloral hydrate in those special affections of the fifth pair of nerves. In cardiac affections morphia subcutaneously has great advantages and anylene hydrate also deserves a prominent place. In diseases of the lungs Sulphonal and Amylene hydrate are the drugs that I prefer. Urethane might also be advantageously tried.

Where delirium ~~tremens~~ and sleeplessness are combined as in delirium tremens many of the newer hypnotics fail and I prefer Bromide of Potassium by itself or in combination with Chloral hydrate and in violent cases hyoscine hypodermically.

Before closing I would emphasize the possibility that synthetic chemistry may yet introduce us to some drug which is superior to all those included in this list, for almost every month we hear of some fresh substance having been produced which is passed on by the chemist for the physiologist or therapist to experiment with and when we look back a few years and see the rapid strides which this newer pharmacopoeia has made we cannot but recognize the possibility - nay we may even say the great probability - that the future will give us such a substance; for among the list of hypnotics which I have endeavoured to analyse therapeutically, the majority belong to this new era.

I have endeavoured in this thesis to review all those substances which are hypnotic in their action, although I have necessarily omitted a few whose hypnotic properties are so feeble that they cannot claim attention even in a dissertation such as this, and if I have added anything to what has been generally known concerning these bodies I shall have

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at least advanced the cause of medical science somewhat.

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